Remarks

These remarks are in response to the Office Action dated October 2, 2002. Claims 5, 6 and 28 have been canceled. Claims 1, 10-13, 25, 26 and 29-50 have been amended. Support for the amended claims can be found throughout the specification. Specifically, support for a marker sequence that "effects the expression of an endogenous gene" can be found at page 18, lines 11-23, of the specification. No new matter has been added. Attached is a marked-up version of the changes being made by the current amendment.

In addition, Applicants attach hereto 1) a copy of the substitute combined Declaration and Power of Attorney, mailed August 30, 2002; and 2) a copy of the return post card received from the Office indicating receipt of the aforementioned Declaration.

Claims 1-3, 7, 9-26 and 29-50 are pending and at issue. Applicant respectfully requests reconsideration of the present application.

I. Objection

Claim 50 is objected to because a clean copy of the amended claim was not included in the previous response. Applicants provide a clean copy of claim 50 in the present response.

II. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-3, 5-7, 9-26, 28-46 and 50 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the relevant art to screen for genes that modulate polyglutamine toxicity in any and all species of

Drosophila using any and all transposable elements. This rejection is moot with regard to canceled claims 5, 6 and 28.

While Applicants respectfully traverse this rejection, Applicants note that the claims have been amended to recite "D. melanogaster" and "P" transposable element. In view of these amendments Applicants request that this rejection under 35 U.S.C. §112, first paragraph be withdrawn.

Claim 50 stands rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to disclose how to detect polyglutamine toxicity in a single cell. While Applicants respectfully traverse this rejection, Applicants note that claim 50 has been amended to delete the recitation of "in one or more cells or tissues." In view of the amendment to the claim, Applicants request that this rejection under 35 U.S.C. §112, first paragraph be withdrawn.

III. Rejections Under 35 U.S.C. §102(b)

Claims 26, 28, 32-34, 37, 39-41 and 50 stand rejected under 35 U.S.C. §102(b) as anticipated by Warrick et al. as evidenced by Paulson et al. because the cited reference of Warrick allegedly teaches the transgenic Drosophila claimed in the instant application. This rejection is moot with regard to canceled claim 28. Applicants respectfully traverse this rejection as it may apply to the amended claims.

Claims 26 and 50 have been amended to recite a polyglutamine sequence "comprising at least 100 contiguous glutamine residues." Warrick teaches a polyglutamine sequence of, at most, 78 residues (page 940, column 1, second paragraph). Paulson teaches a polyglutamine sequence of, at most, 84

residues (page 334, column 1, line 2). In view of the amendment specifying a polyglutamine sequence "at least 100 residues in length", Applicant respectfully submits that Warrick et al., even as evidenced by Paulson et al., fails to teach each element of the pending claims and therefore fails to anticipate the claims. Accordingly, Applicants respectfully requests that this rejection be withdrawn.

IV. Rejections Under 35 U.S.C. §103

Claims 1, 5-7, 9-14, 17-26 and 42 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Warrick et al., in view of Rorth et al. This rejection is moot with regard to canceled claims 5 and 6. Applicants respectfully traverse this rejection as it may apply to the amended claims.

To establish a prima facie case of obviousness, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The Examiner states that the motivation to combine the references is derived from the teachings of Warrick and Rorth. The Examiner cites to page 940 of Warrick which states, in part, that their results "provide a valuable system with which to identify additional genes that can mitigate neurodegeneration." Applicants note that this passage refers to the identification of P35, an exogenous, viral-derived suppressor of apoptosis, as a suppressor of neurodegeneration in Drosophila resulting from polyglutamine toxicity. The method used by Warrick to identify P35 as a suppressor of polyglutamine toxicity includes selecting the known P35 nucleic acid sequence for introduction in to the germline of a Drosophila. Drosophila

expressing the exogenous P35 sequence are then crossed with Drosophila genetically engineered to exhibit polyglutamine toxicity. Progeny exhibiting suppressed polyglutamine toxicity are subsequently identified.

In contrast to the presently claimed method, Warrick fails to teach or describe a method that requires identifying an endogenous gene the expression of which is effected by the insertion of a marker sequence (see claim 1, part b). The effect of the insertion can confer increased or decreased polyglutamine toxicity in an organism, as recited in claim 1, part e). Indeed, while Warrick may teach a method of identifying the effect of expressing a known, non-native gene (i.e., exogenous) on polyglutamine toxicity in Drosophila, he certainly fails to teach or suggest a method of identifying native Drosophila genes not previously associated with modulation of polyglutamine toxicity as targets for modulating polyglutamine toxicity.

Applicant submits that Warrick et al. describes a method of screening for modulation of polyglutamine toxicity through expression of an exogenous nucleic acid sequence but fails to describe a method of screening for modulation of polyglutamine toxicity through expression of an endogenous nucleic acid sequence, as presently claimed. The cited reference of Rorth was published at least 15 months prior to the date that Warrick submitted his paper for publication (i.e., October, 1996, vs. February 24, 1998). Despite the availability of Rorth, Warrick never suggests the possibility of identifying endogenous drosophila genes that effect polyglutamine toxicity via a method even remotely related to the method described in Rorth. In fact, Warrick fails to even cite the Rorth publication. If, as

alleged by the Examiner, one skilled in the art of molecular biology would have been "motivated" by the teachings of Warrick and Rorth to combine the references and arrive at Applicants invention, why was Warrick not similarly "motivated" by his own data to at least mention the possibility of using a method similar to that described by Rorth in order to screen for suppression of polyglutamine toxicity?

Finally, the claimed method has been successfully used to identify and isolate at least 3 genes that modulate polyglutamine toxicity in Drosophila (see page 23, lines 24-26 of the specification). Two of the genes, TPR2 and MLF, were never previously identified in Drosophila. The third gene, HDJ1, was never previously associated with modulation of polyglutamine toxicity in any organism. The fact that the inventors were the first to identify these genes using the claimed method argues that other skilled artisans were not motivated to combine the references in such a way as to achieve the claimed invention. Had the skilled artisan been so motivated, and if the art of screening for genes that effect polyglutamine toxicity was sufficiently predictable such that he had a reasonable expectation of success, then the skilled artisan should have achieved the same success as the present inventors. However, this did not and has not occurred.

For the above reasons, Applicant maintains that there is no suggestion to combine the references in the manner suggested by the examiner to achieve the claimed invention. Accordingly, applicant respectfully requests that this rejection be withdrawn.

In summary, for the reasons set forth herein, Applicants maintain that claims 1-3, 7, 9-26 and 29-50 clearly and patentably define the invention. Applicants request that the Examiner reconsider the various grounds set forth in the Office Action and allow the claims which are now pending. If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' representative can be reached at (858) 678-5070. A check for a one month extension of time is enclosed. Please charge any additional fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 1/8/03

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Version with markings to show changes made

In the claims:

Claims 5, 6 and 28 have been canceled.

Claims 2, 3, 7, 9 and 14-24 are reiterated for the convenience of the Examiner.

Claims 1, 10, 11-13, 25, 26 and 29-50 have been amended as follows:

1. (Twice Amended) A method of screening for genes that modulate polyglutamine toxicity comprising:

(a) providing a first [Drosophila] *D. melanogaster* expressing a polyglutamine sequence, wherein the sequence produces polyglutamine toxicity in the Drosophila;

(b) breeding the first [Drosophila] *D. melanogaster* to a second [Drosophila, wherein the second Drosophila has] *D. melanogaster* comprises a marker sequence inserted into its germline such that the marker sequence effects the expression of an endogenous gene, wherein the marker sequence comprises 1) an inducible upstream activating sequence, 2) a minimal promoter sequence and 3) 5′ and 3′ P transposable elements;

(c) producing progeny from the breeding of the first [Drosophila] *D. melanogaster* with the second [Drosophila] *D. melanogaster*;

(d) screening the progeny for increased or decreased polyglutamine toxicity relative to the first [Drosophila] *D. melanogaster* thereby identifying a progeny having increased or decreased polyglutamine toxicity; and

(e) identifying one or more genes operationally-associated with the marker sequence, or having an insertion of the marker sequence, that confers increased or decreased polyglutamine

toxicity in the progeny having increased or decreased polyglutamine toxicity.

2. The method of claim 1, further comprising identifying a mammalian homologue of the gene of claim 1.

3. The method of claim 2, wherein the mammalian homologue comprises a human homologue.

5. (Canceled) The method of claim 1, wherein the Drosophila is Drosophila melanogaster.

6. (Canceled) The method of claim 1, wherein the transposable element comprises a P transposable element.

7. The method of claim 1, wherein the marker sequence comprises a polynucleotide sequence that disrupts or alters expression of one or more genes near the sequence.

9. The method of claim 1, wherein the inducible upstream activating sequence increases or decreases expression of one or more operationally-associated gene(s).

10. (Twice Amended) The method of claim 1, wherein the second [Drosophila] *D. melanogaster* is selected from a group of two or more animals having markers inserted into different locations of its genomic DNA.

11. (Twice Amended) The method of claim 10, wherein the second [Drosophila] *D. melanogaster* is selected from a group of 10 to 100, 100 to 500, or 500 or more of the animals.

12. (Twice Amended) The method of claim 1, wherein the second [Drosophila] *D. melanogaster* is selected from a library of animals having markers inserted at random locations of their genomic DNA.

13. (Twice Amended) The method of claim 12, wherein the library [of Drosophila] is generated by random P element insertion.

14. The method of claim 1, wherein the polyglutamine sequence comprises a sequence having between about 35 to 50, or between about 50 to 100 glutamine residues.

15. The method of claim 1, wherein the polyglutamine sequence comprises a sequence having between about 100 to 150 glutamine residues.

16. The method of claim 1, wherein the polyglutamine sequence comprises a sequence having about 150 or more glutamine residues.

17. The method of claim 1, wherein the polyglutamine sequence further comprises a tag.

18. The method of claim 17, wherein the tag comprises an epitope tag.

19. The method of claim 18, wherein the epitope tag comprises a hemagglutinin sequence.

20. The method of claim 1, wherein the polyglutamine sequence is encoded by a polynucleotide containing a plurality of CAGs, CAAs or a combination thereof.

21. The method of claim 20, wherein expression of the plurality of CAGs, CAAs or combination thereof is conferred by a constitutive, regulatable or tissue specific expression control element.

22. The method of claim 21, wherein the regulatable element comprises an inducible or repressible element.

23. The method of claim 21, wherein the regulatable element comprises a GAL4 responsive sequence.

24. The method of claim 21, wherein the tissue specific element confers neural, retinal, muscle or mesoderm cell expression.

25. (Twice Amended) A progeny [Drosophila] *D. melanogaster* produced by the method of claim 1.

26. (Twice Amended) A transgenic [Drosophila] *D. melanogaster* comprising a transgene containing a plurality of CAG's and at least one CAA sequence encoding a polyglutamine repeat sequence, wherein the repeat comprises at least 100 contiguous glutamine residues.

28. (Canceled) The Drosophila of claim 26, wherein the Drosophila is Drosophila melanogaster.

29. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein the number of CAG's to CAA's is in ratio of between about 1:1 and 2:1.

30. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein the number of CAG's to CAA's is in ratio of between about 2:1 and 5:1.

31. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein the number of CAG's to CAA's is in ratio of between about 5:1 and 10:1.

32. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein the number of CAG's to CAA's is in ratio of between about 10:1 and 50:1.

33. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein expression of the polyglutamine sequence is conferred by a constitutive, regulatable or tissue specific expression control element.

34. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 33, wherein the tissue specific expression control element confers neural, retinal, muscle or mesoderm cell expression.

35. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 33, wherein the tissue specific expression control element

comprises an Appl or rhodopsin 1 promoter or GLASS transcription factor element.

36. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein the polyglutamine sequence is between about 30 and 50 amino acids in length.

37. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein the polyglutamine sequence is between about 50 and 100 amino acids in length.

38. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein the polyglutamine sequence is between about 100 and 200 amino acids in length.

39. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein the polyglutamine sequence is between about 50 and 200 amino acids in length.

40. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein the polyglutamine sequence further comprises a tag.

41. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein polyglutamine toxicity is produced in one or more tissue or organs of the animal.

42. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 26, wherein the [animal] Drosophila further comprises a marker sequence inserted into its genomic DNA, wherein the marker is located adjacent to a gene or inserted into a gene whose

expression or activity increases or decreases polyglutamine toxicity in the animal, and wherein the marker sequence comprises an inducible upstream activating sequence, a minimal promoter sequence and 5′ and 3′ P transposon elements containing terminal inverted repeats.

43. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 42, wherein the marker sequence is near or inserted into a gene containing a J domain.

44. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 43, wherein the gene is HDJ1.

45. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 43, wherein the gene is TPR2.

46. (Twice Amended) The [Drosophila] *D. melanogaster* of claim 43, wherein the marker sequence is near an MLF gene.

50. (Twice Amended) A method of producing a transgenic [Drosophila] *D. melanogaster* characterized by suppressed polyglutamine toxicity comprising:

(a) transforming a [Drosophila] *D. melanogaster* embryo or fertilized egg with a transgene comprising a plurality of CAA and CAG sequences encoding a polyglutamine sequence comprising at least 100 contiguous glutamine residues [having a length sufficient to produce polyglutamine toxicity in the Drosophila produced from the embryo or fertilized egg]; and

(b) selecting a [Drosophila] *D. melanogaster* that exhibits polyglutamine toxicity [in one or more cells or tissues].